OXADIAZON

109001

Toxicology Disciplinary Chapter for the Reregistration Eligibility Decision Document

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1.0 HAZARD CHARACTERIZATION

Oxadiazon is a selective pre-emergent herbicide of the oxadiazole class. Like other oxadiazoles, it displays light-dependent phytotoxicity through the inhibition of protoporphyrinogen oxidase. Accumulation of protoporphyrin IX following exposure to oxadiazon has been demonstrated in plants, yeast and mouse liver mitochondria. At present, there are no registered food or feed uses. Aventis CropScience USA is supporting use of oxadiazon on golf courses, ornamentals, apartment/condo lawns, athletic fields, parks, playgrounds and cemeteries. The database for oxadiazon is largely complete and provides sufficient information to characterize toxicity. The only data gap that has been identified at this time is the submission of a 28-day inhalation study (OPPTS No. 870.3465). This study was not a guideline requirement for oxadiazon, but has been requested by the Agency because some currently registered products of oxadiazon are spray formulations.

In acute studies, oxadiazon is only slightly toxic (Toxicity Categories III or IV) with an oral LD_{50} >5000 mg/kg, a dermal LD_{50} >2000 mg/kg and an inhalation LC_{50} > 1.94 mg/L. Oxadiazon is mildly irritating to ocular tissue and negligibly irritating to the skin (both Toxicity Category III) and is not a dermal sensitizer.

The major target organ of oxadiazon is the liver. Effects were consistent among the species tested (rat, dog, mouse) in both subchronic and chronic studies and typically included enlarged livers (presumably due to the peroxisomal proliferating activity of oxadiazon), along with increases in serum clinical chemistry parameters associated with hepatotoxicity such as alkaline phosphatase and serum aspartate or alanine aminotransferase. Findings in rats and mice included fatty changes, pigmented Kupffer cells and bile canaliculi and bile duct proliferation, periacinar swelling and pallor, increased acidophilic cells, hyperplasia and hepatocellular necrosis. No treatment-related microscopic lesions were observed in the subchronic dog study and findings in the chronic study were only observed at the HDT (200 mg/kg/day), where only 2 animals/sex were assigned and 1 female was sacrificed in moribund condition. These findings included increased liver weight and hepatocellular histopathology (centriacinar vacuolation, periacinar apoptosis and inflammation). The hematopoietic system also appeared to be a target of oxadiazon in all three species, based on mild anemia (reductions in RBC, hematocrit and/or hemoglobin). This is consistent with its ability to inhibit protoporphyrinogen oxidase, an enzyme involved in the synthesis of both heme and chlorophyll. In addition to effects on the liver, increased pigmentation in the kidney was observed in rats, along with increased BUN and kidney weights. Although a dose-dependent increase in thyroid weight was observed in the dog subchronic oral toxicity study and at the HDT of the chronic dog studies, treatment-related changes in thyroid weights or gross/microscopic observations were not observed in other studies (thyroid hormones were not evaluated). In general, males appeared to be slightly more sensitive to oxadiazon than females.

Oxadiazon is not readily absorbed by the skin. In a rat dermal absorption study, up to ≈9% of the applied dose was absorbed after 10 hours of exposure. The 21-day rabbit dermal toxicity study supports low dermal absorption: no toxicity was observed at the limit dose of 1000 mg/kg/day.

Following long-term dietary administration, oxadiazon caused an increased incidence of hepatocellular adenoma and carcinoma in rats and mice. Consistent findings were reported in a total of 4 acceptable studies in 2 species (2 mouse and 2 rat studies). A third mouse study was unacceptable, although increased hepatocellular tumors were also observed in mice of both sexes. In CD-1 mice, statistically significant increases of hepatocellular adenoma and combined adenoma/adenocarcinoma were observed at all dose levels tested ($\geq$100 ppm) in both males and females. The incidence of hepatocellular carcinoma was increased at all doses in males but only at the two highest doses in females. The highest dose tested exceeded the MTD for males, based on excessive mortality. In ICR-JCL mice, adenomas, carcinomas and combined adenomas/carcinomas were increased in males at the highest 2 dose levels but only at the highest dose level in females. In SPF Wistar rats, the incidence of hepatocellular adenomas , carcinomas and combined adenomas/carcinomas was increased in males only. A second study in F344 rats showed a treatment-related increase in the incidence of hepatocellular carcinoma and combined adenoma/carcinoma only in males. A classification of "likely to be carcinogenic to humans" was assigned by the HED Cancer Assessment Review Committee using the EPA Draft Guidelines for Carcinogen Risk Assessment of July, 1999. A quantitative risk (Q_1*) of 7.11×10^{-2} $(mg/kg/day)^{-1}$ was calculated as the most potent unit risk, based on the incidence of male mouse liver adenoma and/or carcinoma combined tumor rates in the ICR-JCL mouse.

In a special mechanistic study in rats, oxadiazon induced peroxisomal proliferation (based on liver enlargement, peroxisomal enzyme induction and electron microscopy) after a 14-day dietary administration. Some peroxisomal proliferator compounds are known to be liver carcinogens, but the HED Mechanism of Toxicity Assessment Review Committee (MTARC) determined that there are insufficient data available to support this as a mechanism of carcinogenicity for oxadiazon due to insufficient data showing hepatocellular proliferation, lack of concordance between the enzyme induction dose-response and tumor formation and an unexplained decrease in catalase, which is normally significantly increased by peroxisomal proliferator compounds.

Oxadiazon did not show mutagenic potential in any *in vitro* assays with bacteria (*S. typhimurium* and *E. coli*) or mammalian cells (TK +/-mouse lymphoma cells), did not show clastogenic potential in the *in vitro* Chinese hamster ovary cell chromosomal aberration assays and did not induce unscheduled DNA synthesis in cultured primary rat hepatocytes. However, a dose-related increase in transformation frequencies was observed in an *in vitro* Syrian hamster kidney BHK21 C13/HRC1 cell transformation assay.

Significant fetal toxicity (fetal loss due to resorptions and post-implantation loss, decreased fetal weight, skeletal variations) was observed in developmental toxicity studies in both rats and rabbits. These fetal effects occurred at the same dose levels at which slight maternal toxicity (decreased weight gain/weight loss) were observed. Offspring survival effects were also observed in the rat two-generation reproduction study. No toxicity was reported at the lowest dose tested; however, in the range-finding study at higher dose levels, fetal and neonatal survival were also sharply reduced. The decreased neonatal survival was due at least in part to effects on lactation, based on findings of inactive mammary glands in the dams at necropsy. It is likely that neonatal

loss may have resulted from starvation and would, therefore, be an effect of direct maternal toxicity. Inactivity of the mammary tissue as a possible effect of endocrine disruption was considered but was not found to be likely since there was no evidence from any other study in the database suggesting endocrine disruption. No fetal malformations were observed in the rat or rabbit developmental toxicity studies; however, some skeletal variations (delayed ossification, asymmetric pelvis) were reported. The above findings indicate that there is neither qualitative nor quantitative evidence of increased susceptibility of rats or rabbits following *in utero* or postnatal exposure to oxadiazon.

Neurotoxicity studies are not required for oxadiazon because no clinical signs of toxicity suggestive of neurobehavioral alterations nor evidence of neuropathological effects were observed in any of the available toxicity studies. There was no evidence for neurodevelopmental potential of oxadiazon in the rat and rabbit developmental toxicity studies, nor in the rat two-generation reproductive toxicity study.

In a rat metabolism/pharmacokinetic study, oxadiazon was extensively metabolized, primarily via hydroxylation and glucuronide conjugation. However, the benzene and pyrozolidine rings were not modified. Eighteen (18) metabolites were identified in the urine and feces, of which 4 urinary and 5 fecal metabolites were present at levels greater than 1% of the dose. After 7 days, $\geq$83% of the administered dose was excreted in the urine and feces (total recovery $\geq$94%) for all dose groups. Females excreted more radioactivity in the urine than males. The excretion of radioactivity into the urine and the feces was sex dependent and the tissue residues were very low in all tissues except liver and fat. Low doses (5 mg/kg, single or multiple) of oxadiazon were completely absorbed, metabolized and excreted in the urine and feces and virtually no free oxadiazon was found in the urine. At this dose, the rates and routes of excretion of radioactivity were similar. At high dose (500 mg/kg), the rate of excretion was affected but the route was not. Intact oxadiazon was present in feces only and was dose-related: at the high dose, more than 53% of the administered radioactivity was intact oxadiazon in the feces; at 5 mg/kg, not more than 4.8% of the dose was intact oxadiazon in the feces.

2.0 REQUIREMENTS

The requirements (CFR 158.340) for non food/feed (turf) uses for oxadiazon are shown below in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table 1. Data requirements for Reregistration of Oxadiazon

Test	Technical	
	Required	**Satisfied**
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rodent)	yes	yes
870.3150 Oral Subchronic (nonrodent)	yes	yes
870.3200 21-Day Dermal	yes	yes
870.3250 90-Day Dermal	no	--
870.3465 90-Day Inhalation	yes[1]	no
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (nonrodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	yes	yes
870.4100b Chronic Toxicity (nonrodent)	yes	yes
870.4200a Oncogenicity (rat)	yes	yes
870.4200b Oncogenicity (mouse)	yes	yes
870.4300 Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375 Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5550 Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a Acute Delayed Neurotox. (hen)	no	--
870.6100b 90-Day Neurotoxicity (hen)	no	--
870.6200a Acute Neurotox. Screening Battery (rat)	no	--
870.6200b 90 Day Neuro. Screening Battery (rat)	no	--
870.6300 Develop. Neuro	no	--
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	no[2]	yes
Special Studies for Ocular Effects		
Acute Oral (rat)	no	--
Subchronic Oral (rat)	no	--
Six-month Oral (dog)	no	--

1 A 90-day inhalation study is not a guideline requirement for oxadiazon. However, a 28-day inhalation study has been requested by the Agency because some of the currently registered products are spray formulations.

2 This study was not required by the Agency, but was submitted as additional information for oxadiazon.

3.0 DATA GAPS

There are no guideline required data gaps. However, HIARC has recommended the submission of a 28-day inhalation toxicity study in the rodent because some of the currently registered products are spray formulations.

4.0 HAZARD ASSESSMENT

4.1 Acute Toxicity

Adequacy of data base for acute toxicity: The data base for acute toxicity is considered complete. No additional studies are required at this time. The acute toxicity of oxadiazon is low by all potential routes of exposure (Toxicity Category IV, oral and III, dermal and inhalation). Primary eye irritation is mild and skin irritation is negligible (both Category III). Oxadiazon did not show potential for dermal sensitization in a Buehler test.

The acute toxicity data on oxadiazon technical is summarized in Table 2.

Table 2. Acute Toxicity Data on Oxadiazon

Guideline No./ Study Type	MRID No.	**Results**	**Toxicity Category**
870.1100 Acute oral toxicity (rat)	41866501 (97.5% a.i.)	LD_{50} >5000 mg/kg ♂, ♀ combined	IV
870.1200 Acute dermal toxicity (rabbit)	41866502 (97.5% a.i.)	LD_{50} >2000 mg/kg, ♂, ♀ combined	III
870.1300 Acute inhalation toxicity (rat)	41866503 (93.7% a.i.)	LC_{50} >1.94 mg/L ♂, ♀ combined	III
870.2400 Acute eye irritation (rabbit)	41866504 (97.5% a.i.)	Mild irritant to ocular tissues	III
870.2500 Acute dermal irritation (rabbit)	41866505 (97.5% a.i.)	Negligibly irritating to skin	III
870.2600 Skin sensitization (guinea pig)	41230401 (93.7% a.i.)	Not a dermal sensitizer (Buehler test)	--
870.6200a Acute neurotoxicity screening battery (rat)	ND	--	--

ND No data - not required for oxadiazon.

4.2 Subchronic Toxicity

Adequacy of data base for subchronic toxicity: The data base for subchronic toxicity is considered complete with respect to the guideline requirements for a non-food/feed use. However, the HIARC has recommended the submission of a 28-day inhalation toxicity study because some of the currently registered products are spray formulations. In the rat, liver effects from subchronic exposure included increased weight, increased ALT, AST, alkaline phosphatase and BUN, and microscopic findings such as increased brown pigmentation of Kupffer cells and bile canaliculi, variable hepatocyte size and staining and necrosis. In addition, decreased red blood cell parameters, increased splenic hematopoietic activity and vacuolization of cells of the adrenal gland and the kidney were observed. In the dog, increased liver and thyroid weights and serum levels of alkaline phosphatase and ALT were reported, but no liver pathology or hematological effects were observed at the doses tested. No toxicity following 21 consecutive daily dermal exposures was observed in rats exposed up to the limit dose of 1000 mg/kg/day.

In addition to the Executive Summaries provided below, subchronic toxicity studies are summarized in capsule form in Section 9.0 (Appendix), Table 9.1.2 (toxicity profile table).

870.3100 90-Day Oral Toxicity - Rat

In a 90-day subchronic oral toxicity study (MRID 00111804), oxadiazon as RP 17623 (tech., 98.2% a.i.) was administered to CD rats (10/sex/dose) at dietary levels of 0, 25, 100 or 1000 mg/kg/day) for 13 weeks. Clinical signs, body weights and food consumption were determined weekly. At 4 and 13 weeks, hematology, clinical chemistry and urinalysis determinations were performed. Cholinesterase activity was also measured in erythrocytes at 13 weeks. Necropsy, organ weights and histology examinations were performed at 13 weeks.

Mortality was confined to one high-dose male at week 10 and one high-dose female at week 12. Other clinical signs noted at 1000 mg/kg/day were: hunched appearance, urine stains, rapid respiration, yellow skin pigmentation and loss of coordination (both sexes). Body weight (-13 and -49%) was significantly decreased in males at 100 and 1000 mg/kg/day; respectively, and in females (-21%) at 1000 mg/kg/day. Food consumption was significantly reduced for both sexes at the high dose. Affected hematological parameters included: slight decreases in hematocrit, hemoglobin and erythrocyte count for high-dose males and females (13 weeks). ALP, total bilirubin, SGPT (4 and 13 weeks) BUN and SGOT (13 weeks) were increased in high-dose males and females. Mid-dose males also had increased ALP, SGOT and SGPT values. There was no effect on cholinesterase activity. Significantly increased absolute and relative liver weights were seen in males and females receiving 100 and 1000 mg/kg/day. Microscopic changes were also apparent for intermediate and high-dose males and females. At 1000 mg/kg/day (males and females) and 100 mg/kg/day (males), the liver contained brown pigment in the Kupffer

cells and bile canaliculi, marked variability in cell size and staining properties of the hepatocytes and necrotic hepatocytes. The adrenals contained cytoplasmic vacuolation of the zona fasciculata, vacuolation and hypertrophy of cells in the zona reticularis and increased vacuolation of the zona glomerulosa (males and females at 1000 mg/kg/day). Also at 1000 mg/kg/day, the spleen showed increased hematopoietic activity and brown pigmentation; granular pigmentation and vacuolation were reported for the kidneys. No significant effects were seen at 25 mg/kg/day. **The LOAEL is 100 mg/kg/day, based on decreased body weight, increased liver weight, hematological changes and clinical chemistry and pathological changes associated with damage to the livers of males and females; the NOAEL is 25 mg/kg/day**.

This 90-day subchronic oral toxicity study in the rat is **Acceptable/guideline** and satisfies the guideline requirement for a subchronic toxicity study **(870.3100)** in rodents.

870.3100 90-Day Oral Toxicity - Mouse

A 90-day oral toxicity study in the mouse was not submitted.

870.3150 90-Day Oral Toxicity - Dog

In a subchronic oral toxicity study (MRID 00111805), oxadiazon (tech., 98.2% a.i.) was administered to 4 Beagle dogs/sex/dose in the diet for the initial 3 weeks of the study at concentrations of 0, 1000, 4000 or 10,000 ppm. Due to unpalatability of the diets, the test material was administered via gelatin capsule from weeks 4 to 13 at 0, 25, 100 or 1000 (limit dose) mg/kg/day. The high-dose group received 250 mg/kg/day by gelatin capsule during week 4 instead of 1000 mg/kg/day. It was stated that a single high-dose male died during week 4 due to incidental causes and was replaced with another dog; it was not specified if the replacement animal was treated or untreated prior to week 4. No statistical analyses were provided.

At 25 mg/kg/day, increased abs/rel thyroid weights were observed in males (+18/+34%). At 100 mg/kg/day, increased alkaline phosphatase during weeks 4 and 13 (+16 to +41%) in the males only; increased aspartate aminotransferase during week 13 (+14 to +26%) in males and females; increased abs/rel thyroid weights in males (+26%/+35%); increased relative thyroid weights in females (+34%); increased abs/rel liver weights (males +15%/+28%) and relative liver weights in females (+28%) were observed. At 1000 mg/kg/day, increased alkaline phosphatase during weeks 4 and 13 (+23 to +181%) in the males; increased aspartate aminotransferase during weeks 4 and/or 13 (+10 to +80%) in males and females, increased abs/rel liver weights (+24%/+53%, males and +60%/+34%, females) and increased abs/rel thyroid weights (+30%/+59%, males and +23%/+39%, females) were observed. Large reductions in food consumption were noted in the high dose males during the first 3 weeks of treatment (-36 to -50%). In the treated females, decreased food consumption was observed during the first 3 weeks of treatment at the low- (-4 to -20%), mid- (-23 to -44%), and high-dose levels (-31 to -45%). These decreases

were attributed to unpalatability of the test substance in the diet; after changing to capsule administration, food consumption did not show a clear dose-dependent decrease. No treatment-related changes in body weights, clinical signs of toxicity, overall body weight gains, hematology, urinalysis, erythrocyte cholinesterase levels, gross or microscopic pathological findings were observed. **The systemic toxicity LOAEL for this study is ≤25 mg/kg/day, based on increased thyroid weights in males. The systemic toxicity NOAEL for this study is <25 mg/kg/day.**

This study is classified as **Acceptable/guideline (870.3150)** and satisfies the requirement for a subchronic oral toxicity study in dogs. Although a NOAEL was not identified in this study, a NOAEL of 5 mg/kg/day was identified in a subsequently conducted chronic oral study in the dog (MRID 41326401; HED Doc. Nos. 008248 and this Doc. No.).

870.3200 21-Day Dermal Toxicity – Rat

In a 21-day dermal toxicity study (MRID 41863602), oxadiazon technical (97.49% a.i., moistened with distilled water) was applied dermally 6 hrs/day, 7 days/week for 3 weeks to 8 male and 8 female New Zealand White rabbits per dose at 0, 100, 500 or 1000 mg/kg/day.

Treatment with oxadiazon technical had no effect on mortality, body weight, body weight gain, food consumption, hematology, clinical chemistry, urinalysis, organ weights or gross necropsy. Dermal irritation (erythema, edema and eschar) was observed in treated and control rabbits. These symptoms first appeared during the second week and persisted throughout the study. Histologically, the skin lesions include acanthosis, hyperkeratosis, acute and chronic dermatitis, acute folliculitis, exudate on the dermal surface, edema and hemorrhage, which are characteristic of chronic inflammation and occlusion. Although a higher incidence of erythema and edema was noticed in the 500 and 1000 mg/kg groups, the significance of these findings is questionable. The investigator overlooked pharmacokinetic principles in conducting the study. The approximate area of the test article treated skin was 25.9, 92.1 and 119.5 cm^2 for the 100, 500 and 1000 mg/kg/day groups, respectively, which indicates that the administered dose (mg/cm^2) was the same in all cases. It is appropriate to apply graded concentrations of the test material to the entire test area (i.e., 10 % of the body surface area, rather than a fraction of the test area). Even though appropriate doses were not tested, the highest level tested reached the **Limit Dose**. The results suggest, therefore, that at the **Limit Dose,** oxadiazon Technical is not an irritant to rabbit skin. **The systemic toxicity and local (dermal irritation) LOAELs are >1000 mg/kg/day and the NOAELs are ≥1000 mg/kg/day.**

This study is classified **Acceptable/guideline** and satisfies the guideline requirement for a 21-day dermal study **(870.3200)** in the rabbit.

4.3 Prenatal Developmental Toxicity

Adequacy of data base for Prenatal Developmental Toxicity: The data base for prenatal developmental toxicity of oxadiazon is considered complete. No additional studies are required at this time. Similar findings were reported in rats and rabbits, although the sensitivity of fetuses to oxadiazon was greater in rats than in rabbits. In rats, fetal toxicity (increased resorptions/post-implantation loss, decreased fetal weight and increased incidence of incomplete ossification in skull and vertebral bones) were reported at 40 mg/kg/day, whereas only slightly decreased during late gestation, due at least in part to the fetal loss at that dose level. In the rabbit, developmental toxicity (increased post-implantation loss and late resorptions, decreased mean fetal weight and increased incidence of bilateral hind-limb flexure) was observed at the highest dose tested (180 mg/kg/day), whereas maternal toxicity (transient weight loss and decreased food consumption during and after treatment) was observed at mid dose (60 mg/kg/day) and higher.

In addition to the Executive Summaries provided below, developmental toxicity studies are summarized in capsule form in Section 9.0 (Appendix), Table 9.1.2 (toxicity profile table).

870.3700a Prenatal Developmental Toxicity Study - Rat

In a developmental toxicity study (MRID 40470202), oxadiazon technical (96.3% a.i.) was administered daily by gavage in 10 ml 1% aqueous methylcellulose vehicle/kg body weight from Gestation Days 6 through 15 to groups of 20 pregnant Sprague-Dawley rats per dose at 0, 3, 12 or 40 mg/kg/day. Pregnant females were examined daily for signs of toxicity and body weights were measured on Gestation Days 0, 3, 6, daily through Day 16 and on Days 18 and 20. Dams were sacrificed on Day 20 and uterine contents were examined.

Very little maternal toxicity was observed at any dose. Small but statistically significant decreases in body weight (-2% less than controls) and body weight gain (-10%) in the high-dose females at Days 16-20 were possibly due to resorptions of fetuses (decreased maternal body weights also observed at $\geq$40 mg/kg/day in the range-finding study). **The maternal toxicity LOAEL is 40 mg/kg/day, based on decreased body weight/weight gain. The maternal toxicity NOAEL is 12 mg/kg/day.**

Treatment-related fetal toxicity at 40 mg/kg/day included: slightly, not statistically significantly increased fetal resorptions (0.7/dam vs. 0.4/dam, controls) and post-implantation loss (12.5% vs. 8.2%, controls) and significantly decreased body weight (-4.5% less than controls). Developmental effects at 40 mg/kg/day were confined to increased incidence of incomplete ossification, primarily in skull and vertebral bones. No effects were seen at lower doses. No treatment-related malformations were observed at the doses tested. Fetal effects seen in this study are considered treatment-related based on the steep dose-response curve (for fetal loss and decreased fetal weight) between 20-60 mg/kg/day in the preliminary range-finding study. Therefore, the effects seen at 40 mg/kg/day are considered a threshold response for oxadiazon under the conditions of the

main study. **The developmental toxicity LOAEL (threshold) is 40 mg/kg/day, based on increased fetal resorptions/postimplantation loss, decreased fetal weight and increased incidence of incomplete ossification. The developmental toxicity NOAEL (threshold) is 12 mg/kg/day**.

This study is classified **Acceptable/guideline** and satisfies the guideline requirement for a developmental toxicity study **(870.3700a)** in the rat.

870.3700b Prenatal Developmental Toxicity Study - Rabbit

In a developmental toxicity study (MRID 40470201), oxadiazon technical (95.6% a.i.) was administered daily by gavage in 5 ml 1% aqueous methylcellulose vehicle/kg body weight from gestation days 6 through 19 to groups of 15 to 19 pregnant New Zealand White rabbits per dose at 0, 20, 60 or 180 mg/kg/day. Pregnant females were examined daily for signs of toxicity and body weights were measured on Gestation Days 0 and 6, on alternate days through day 20 and on days 24 and 28. Dams were sacrificed on Day 29 and uterine contents were examined.

Treatment-related maternal toxicity was observed at 60 mg/kg/day as transient weight loss (-0.01 kg vs. 0.10 kg gain, controls; $p<0.05$) and slightly decreased food consumption during the first half of treatment (-15% less than controls, treatment days 6-12; not statistically significant). These effects were more pronounced at 180 mg/kg/day and showed statistically significant reductions in weight gain and marked reductions in food consumption during and after treatment. **The maternal toxicity LOAEL is 60 mg/kg/day, based on transient weight loss and decreased food consumption during treatment. The maternal toxicity NOAEL is 20 mg/kg/day.**

Treatment-related fetal toxicity at 180 mg/kg/day included: increased postimplantation loss and late resorptions (18.85% vs. 8.6%, controls; $p<0.05$), decreased mean fetal weight (-10%) and increased incidence of bilateral hind-limb flexure (4.2% of fetuses, 3 litters affected vs. 0%, controls). Marginal developmental effects at 180 mg/kg/day were: increased incidence of rib abnormalities, delayed/incomplete ossification in several bones and asymmetrical pelvis. No effects were seen at lower doses and there were no treatment-related malformations observed at any dose tested. **The developmental toxicity LOAEL is 180 mg/kg/day, based on increased postimplantation loss, decreased mean fetal weight, increased bilateral hind-limb flexure and possibly delayed/incomplete ossification of several bones. The developmental toxicity NOAEL is 60 mg/kg/day.**

This study is classified **Acceptable/guideline**; it satisfies the guideline requirement for a non-rodent developmental toxicity study **(870.3700b)** in the rabbit.

4.4 Reproductive Toxicity

Adequacy of data base for Reproductive Toxicity: The data base for reproductive toxicity is considered complete. No additional studies are required at this time. In the rat two-generation reproductive toxicity study, no maternal, offspring or reproductive effects were reported at any dose tested up to 200 ppm (15.5 mg/kg/day). However, in the range-finding study at ≥400 ppm (38 mg/kg/day), significant toxicity to the offspring (fetal/neonatal mortality) and the dams (inactive mammary tissue, decreased gestational weight, due at least in part to fetal mortality) was observed. The neonatal mortality was probably related to the mammary tissue effects in the dams.

In addition to the Executive Summaries provided below, the reproductive toxicity study is summarized in capsule form in Section 9.0 (Appendix), Table 9.1.2 (toxicity profile table).

870.3800 Reproduction and Fertility Effects - Rat

In a 2-generation reproduction study (MRID 41239801; range-finding study MRID 41240301) oxadiazon (96.6% a.i.) was administered in the diet continuously to CD rats (30 rats/sex/dose) at 0, 20, 60 or 200 ppm (equivalent to an average daily intake [M/F] of 0, 1.50/1.84, 4.65/5.63 or 15.50/18.20 mg/kg/day, average of P and F_1 generation premating food consumption). Dose levels were selected based on the results of the 1-generation range-finding study, which tested at 0, 50, 100, 200, 400 or 800 ppm (6 animals/sex/dose, 4 weeks premating exposure). The P animals were exposed to the test substance beginning at approximately 6 weeks of age for 14 weeks prior to mating and continuing until sacrifice after weaning (post-partum day 25). F_1 pups selected (30/sex/dose) to produce the F_2 generation were exposed to the same dosage as their parents beginning at postnatal day (PND) 25 for 14 weeks premating and continuously throughout the rest of the study until weaning of the F_2 offspring (postpartum day 25). Liver, kidneys, ovaries, uterus, prostate, epididymis, testes and seminal vesicles were weighed and examined for gross/microscopic pathology. Mammary gland, pituitary and vagina were examined for pathological changes. The 1-generation range-finding study tested in 6 dams/dose group at dietary concentrations of 0, 50, 100, 200, 400 or 800 ppm (0, 5/5, 9/9, 19/19, 36/38 or 67/75 mg/kg/day, respectively), administered beginning15 days prior to initiation of mating until lactation day 4. No treatment-related findings were reported at ≤200 ppm; effects at 400 and 800 ppm are discussed below.

There was no evidence of treatment-related changes in clinical signs, mortality, body weights or weight gains, food consumption, food efficiency, organ weights or microscopic or macroscopic pathology observed in P or F_1 adults in the main study. Slight liver alterations in F_1 adults at 200 ppm (+6% relative liver weight, females, periacinar hepatocellular hypertrophy, males) were considered an adaptive response. However, at 400 ppm in the range-finding study, markedly decreased gestational weight gain (-34% below controls, primarily after GD 13) was observed (due largely to increased fetal loss). At 800 ppm, decreased maternal weight gain of -38% below controls, also primarily after GD 13, blood in the urine in the cage paper of males and blood in the nares/face/urogenital region of 1 dam were observed. **The LOAEL (main study) for parental toxicity is >200 ppm (15.5 mg/kg/day; HDT in main study); however, a LOAEL of 400 ppm (38**

mg/kg/day), based on decreased gestational weight gain, was observed in the range-finding study. The parental toxicity NOAEL (main study) is ≥200 ppm.

No differences in reproductive parameters in P or F_1 parental animals, nor in F_1 or F_2 offspring viability, clinical signs, body weight or body weight gain, developmental landmarks, auditory or ophthalmological function or macroscopic pathology were observed in the main study. However, in the range-finding study, pronounced reproductive/offspring toxicity at 400 ppm in the 4 dams that littered (5 pregnant) included inactive/pale mammary tissue, reduced litter size and increased gestation length (+1 day). Pre-/perinatal mortality resulted in total litter losses for all dams by day 1 postpartum (17 offspring were examined: 20% late resorptions, 7.7% dead fetus, 73% without milk in stomach). At 800 ppm, 2 dams littered but all were late resorptions; 4 dams that failed to litter had blood in their cage on GD 23 (implantation sites/dam were comparable to controls). **The reproductive/offspring toxicity LOAEL (main study) is >200 ppm (15.5 mg/kg/day; HDT in main study); however, a LOAEL of 400 ppm (38 mg/kg/day), based on inactive mammary tissue and fetal/pup death, was observed in the range-finding study. The reproductive/offspring toxicity NOAEL (main study) is ≥200 ppm.**

This reproductive toxicity study in the rat is classified **Acceptable/guideline (870.3800)** and satisfies the guideline requirement for a multigenerational reproductive toxicity study in rats. Although no significant effects were observed at ≥200 ppm in the main or range-finding studies, pronounced reproductive/offspring toxicity, including complete litter loss, was observed at ≥400 ppm. At the Hazard Identification Assessment Review Committee (HIARC) meeting, held December 7, 2000 (see HED Document No. 014469), it was concluded that the neonatal loss seen at 400 ppm was attributable to maternal effects (*i.e.*, inactive mammary tissue resulting in possible starvation of the pups which was manifested as 73% of the examined offspring without milk in their stomachs). The HIARC further concluded that the inactivity of mammary tissue may have been related to endocrine disruption. However, this finding was not considered to be likely because there was no supporting evidence of possible endocrine disruption observed in any other study in the Oxadiazon database.

4.5 Chronic Toxicity

Adequacy of data base for chronic toxicity: The data base for chronic toxicity is considered complete. No additional studies are required at this time. In the Wistar rat, males were more sensitive to oxadiazon than females and the NOAEL of 10 ppm (0.36 mg/kg/day) was based on centrilobular swelling in male rat liver at 100 ppm (3.5 mg/kg/day). Oxadiazon caused hepatic toxicity, demonstrated by alterations in liver-related blood enzymes (males), liver enlargement and microscopic pathology (hepatocellular swelling and increased acidophilic foci of cellular alteration, brown pigmentation and bile duct proliferation). Liver tumors were also increased by treatment (see Section for details). Mild anemia was observed in males. In addition, oxadiazon caused renal

toxicity (increased BUN, brown pigmentation in the proximal tubular cells and cortical interstitial tissues in both sexes and incidence of chronic nephropathy in males). F344 rats had similar treatment-related effects, including anemia in males, increased liver-related blood enzymes primarily in males, increased urine color and bilirubin/urobilinogen, increased liver and kidney weights, microscopic liver effects such as hypertrophy, fatty change and necrosis and pigmented nephrosis. In the dog, the liver was also the primary target organ, as demonstrated by liver enlargement. Evidence of liver pathology and serum enzyme alterations, increased blood/bilirubin in the urine, increased kidney and thyroid weights (and possibly anemia in 1 female) were observed only at a relatively high dose (200 mg/kg/day) in which only 2/sex dogs were evaluated and 1 female was sacrificed in moribund condition.

In addition to the Executive Summaries provided below, chronic toxicity studies are summarized in capsule form in Section 9.0 (Appendix), Table 9.1.2 (toxicity profile table).

870.4300 Chronic Toxicity/Carcinogenicity – Rat

(1) In a chronic/carcinogenicity toxicity study (MRID Nos. 00149003 [main study]/MRID 00157780 [additional data]), oxadiazon (tech., 99.9% a.i.) was administered to Fischer 344 rats (76/sex/dose) in the diet at dose levels of 0, 10, 100, 1000 or 3000 ppm (mean consumption per group: equivalent to 0, 0.5, 4.8, 50.9 or 163.1 mg/kg/day for males or 0, 0.6, 5.9, 60.9 or 192.7 mg/kg/day for females) for 24 months. Parameters examined included: (1) twice daily observations, (2) weekly body weights and food consumption, (3) ophthalmic examinations (all animals at pretest and 10 rats/group at 6, 12 and 24 months), (4) standard hematology, clinical chemistry and urinalysis (10 rats/group at 6, 12 and 24 months), and (5) gross necropsy, organ weights and histology (10 rats/group at 6 and 12 months and all survivors at 24 months).

There were no effects on mortality. At 1000 and 3000 ppm, clinical signs included emaciation, anemia and brown colored urine; ophthalmic examinations revealed narrowing of the fundus vasculature (males at 1000 ppm and both sexes at 3000 ppm). Significant decreases ($p<0.05$-0.001) in body weight gain were apparent in rats of both sexes receiving 1000 or 3000 ppm and significant decreases in food consumption were recorded for both sexes starting at week 3 (males) and week 6 (females). Consistent hematological findings indicative of anemia at 3000 ppm (both sexes) were: significantly decreases erythrocyte counts, hematocrit, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration. Anemia was also present in males at 1000 ppm and appeared to be less severe in females. Adverse effects on urinalysis parameters were confined to the two highest dose groups (both sexes) and included: urine color, strongly positive bilirubin and urobilinogen. Significantly affected clinical chemistry parameters included: reduced glucose levels (males $\geq$1000 ppm at 6 and 12 months; females 3000 ppm at 6 months); increased total protein (consistent effect only in the females at $\geq$100 ppm and generally at all sampling intervals); increased total cholesterol (males at 1000 ppm and both sexes at 3000 ppm) and increased bilirubin (males $\geq$1000 ppm at 6 and 12 months; females 3000 ppm at 6 months). In addition, significant increases

in GOT, GPT, AP and BUN generally correlated well with liver morphological changes at ≥1000 ppm (males). Similarly, increased absolute and relative liver and kidney weights at ≥1000 ppm (both sexes) correlated well with liver and kidney histopathology effects. At termination, oxadiazion also induced increased absolute and relative liver weights at 100 ppm (females). Non-neoplastic pathology included: hepatocyte changes consisting of progressive alterations from hypertrophy through fatty changes to necrosis were noted in males receiving 1000 and 3000 ppm and females receiving 3000 ppm. Other non-neoplastic changes noted in both sexes were: pigmented nephrosis and fat replacement in the pancreas at 1000 ppm and basophilic changes in the adrenal glands at 3000 ppm. **The LOAEL is 100 ppm (4.8 mg/kg/day) based on increased absolute liver weights in males and females and increased total serum protein in females. The NOAEL is 10 ppm (0.5 mg/kg/day).**

Neoplastic findings were: increased incidences of benign and malignant liver tumors in males at 1000 and 3000 ppm after prolonged exposure to hepatotoxic doses. In addition, there was no decrease in latency for liver neoplasia. Dosing was considered adequate in males and the data support a presumption that the maximum tolerated dose (MTD) lies between 100 and 1000 ppm.

This chronic/carcinogenicity study in the rat is **Acceptable/Guideline** and satisfies the guideline requirement for a combined chronic/carcinogenicity study **(870.4300)** in the rat.

(2) In a chronic/oncogenicity toxicity study (MRID 40993401), oxadiazon (tech., 95.9% a.i.) was administered to SPF Wistar rats (80/sex/dose) in the diet at dose levels of 0, 3, 10, 100 or 1000 ppm (equivalent to 0, 0.106, 0.36, 3.5 or 39 mg/kg/day for males or 0, 0.131, 0.44, 4.2 or 44 mg/kg/day for females) for 104 weeks. Clinical signs were monitored daily. Body weights were determined weekly for the first 26 weeks and biweekly, thereafter; food consumption was determined weekly for 20 rats/group. Groups of 8 rats/sex/group were sacrificed at weeks 26, 52 and 78 and 10 animals/sex/group at 104 weeks were subjected to hematology, biochemistry and urinalysis examinations. All 80 rats/sex/dose were reportedly examined for histopathology. Dose selection was based on a preliminary 4-week range finding study with 10, 100, 1000 or 3000 ppm. At 1000 and 3000 ppm, signs of toxicity included: anemia (males--both groups; females--3000 ppm, only), effects on biochemical parameters associated with hepato-renal disorders (increased GOT, GPT, ALP, BUN, total cholesterol and/or urobilinogen), and liver and kidney weight changes accompanied by a dark color.

There were no adverse effects on mortality, clinical signs or food consumption. Treatment related effects included: decreased body weight gain for high-dose males generally throughout the study; statistically significant body weight losses (-8.9%) were reported for the 10- and 1000 ppm females only at study termination. Hematological parameters significantly affected were: decreased hematocrit and hemoglobin (high-dose males at week 26) and decreased mean corpuscular volume and mean corpuscular hemoglobin (high-dose males at weeks 26, 78 and 104). There were no consistent hematological effects in the

females. The generalized changes in the blood elements of male rats are indicative of anemia which was most evident at week 26. Significantly affected clinical chemistry parameters included: increased LDH, ALT, GOT, GPT, total and direct bilirubin and total cholesterol for high-dose males at week 26; no toxicologically significant effects were seen in the females of any dose group. At 1000 ppm, males also showed increased urobilinogen at week 26. Increased liver weights were seen in high-dose males and females throughout the study and statistically significant increases in kidneys (both sexes) and testis (males) were also consistently seen at 1000 ppm. Non-neoplastic pathology in the liver at 1000 ppm included: increased centrilobular hepatocellular swelling (males and females); increased acidophilic foci of cellular alteration (males); brown pigmentation in the liver (males and females); and bile duct proliferation (males) At 100 ppm, increased centrilobular hepatocellular swelling was also seen in the males. Brown pigmentation in the proximal tubular cells and in cortical interstitial tissue (males and females); and chronic nephropathy (females) were also recorded for the kidneys of high-dose rats. **The LOAEL is 100 ppm (3.5 mg/kg/day) based on centrilobular swelling in the male rat livers; the NOAEL is 10 ppm (0.36 mg/kg/day**).

Neoplastic findings were: increased incidence of liver adenomas in males at 100 ($p<0.05$) and 1000 ppm ($p<0.010$); liver carcinomas were also increased at 1000 ppm in both sexes but not significantly. Dosing was considered adequate in males based on signs of transient anemia, increased serum enzyme activity, bilirubin and liver weight, decreased body weight gain, and pathological changes in the liver (centrilobular hepatocellular swelling and foci of cellular alteration). Females were considered to be tested at a dose below the maximum tolerated dose (MTD). However, since the NOAEL and LOAEL were defined for males (0.36/3.5 mg/kg/day), the hypothetical values for females are expected to be higher. Hence, the NOAEL and LOAEL for males are considered to be protective for females.

The pathology report for this chronic/carcinogenicity study in the rat was considered incomplete; thus, the overall study was listed as Supplementary. At this time, no additional information is being requested because the results are consistent with an acceptable rat chronic/carcinogenicity study (MRID No. 0014003/00157780) that satisfies the guideline requirement. Similarly, the presence of liver neoplasms confirms the evidence of a carcinogenic effect seen in MRID No. 0014003/00157780. After review of the data from this study by the Cancer Assessment Review Committee (CARC), however, it was concluded that this deficiency did not compromise the integrity of the study or the interpretation of the results [see Cancer Assessment Document--Evaluation of the Carcinogenic Potential of Oxadiazon (Third Review), dated April 2001]. Using this rationale, the study is now upgraded and listed as **Acceptable/guideline** and satisfies the guideline requirement for a combined chronic toxicity/carcinogenicity study in the rat **(870.4300)**.

870.4100b Chronic Toxicity - Dog

In a one-year chronic oral toxicity study (MRID No. 41326401), oxadiazon (tech., 94.9%

a.i.) was administered orally via capsules once a day to five groups of Beagle dogs (4 males and 4females/group dosed with 0, 5, 20 or 60 mg/kg/day; 2 males and 2 females dosed with 200 mg/kg/day). Dose selection was based on the findings of a preliminary study showing that dogs could not tolerate 360 mg/kg/day and that minimal changes were seen at 60 mg/kg/day. Parameters examined in all animals included: (1) daily observations; (2) weekly body weights and food consumption; (3) ophthalmic examinations at pretest and week 51; (4) standard hematology (pretest and at weeks 12, 24 and 50), clinical chemistry (pretest and at weeks 24 and 50) and urinalysis; (5) bone marrow analysis at week 52; and (6) gross necropsy, organ weights and histology. Due to the small number of animals tested (2/sex, 1 female sacrificed at week 11) and that they were rejected due to lower body weight from inclusion in the range-finding study, the findings in the 200 mg/kg/day dogs were considered to be supplementary information.

There were no effects on mortality, clinical signs, food consumption, hematology, urinalysis or ophthalmic examinations. At 60 mg/kg/day, clinical biochemical changes in the males (3 of 4) included significant ($p<0.05$) elevations (~ +35%) in aspartate aminotransferase (AST) at all intervals. For females, ALT and AST values were significantly decreased at week 24 (-32% to -40%), an effect not considered of toxicological significance. No other alterations in biochemical parameters were considered to be an effect of oxadiazon. In males, significant increases in relative liver weights were seen at 60 (+39%) and 200 (+61%) mg/kg/day; absolute liver weights were also increased at 60 (+28%) and 200 (+41%) mg/kg/day but statistical significance was not attained. The response was dose-related with weight increases of +7, +23 or +28% (absolute) and +7, +21 and +28% (relative) at 5, 20 or 60 mg/kg/day, respectively. In females, significant increases in absolute liver weight were noted at levels ≥20 mg/kg/day (+35% and +44% at 20 and 60 mg/kg/day, respectively); a nonsignificant +21% increase was seen at 5 mg/kg/day. Relative female liver weights also showed a dose-related response with a +7, +10 or +38% increases at 5, 20 or 60 mg/kg/day, respectively. However, organ weight changes and increased blood levels of AST were not definitively associated with a pathological condition in the liver. At 200 mg/kg/day, one female was sacrificed in moribund condition. Observed effects included pallor, thinness, decreased weight gain, possible anemia (based on hematological changes, brown urine in the sacrificed female and blood/bilirubin in the urine of the surviving female), clinical chemistry alterations (increased ALT, phosphorous; decreased glucose, total cholesterol, protein and potassium), increased liver, spleen, kidney and thyroid weights (also lower testes weights) and hepatocellular histopathology (centriacinar hepatocytic vacuolation, periacinar apoptosis and periacinar inflammation in females). **The systemic toxicity LOAEL is 20 mg/kg/day, based on hepatic toxicity (increased absolute and relative female liver weight accompanied by similar changes in the absolute and relative liver weights for both sexes at 60 mg/kg/day). The systemic toxicity NOAEL is 5 mg/kg/day.**

This study is classified **Acceptable/Guideline** and satisfies the guideline requirement for a non-rodent chronic oral toxicity study **(870.4100b)** in the dog.

4.6 Carcinogenicity

Adequacy of data base for Carcinogenicity: The data base for carcinogenicity is considered complete. No additional studies are required at this time. An increased incidence of hepatocellular neoplasms were observed in both rats (F344 and Wistar) and mice (CD-1 and ICR-JCL). In mice, liver tumor incidence was increased in both sexes, whereas in rats the males were affected.

In addition to the Executive Summaries provided below, carcinogenicity studies are summarized in capsule form in Section 9.0 (Appendix), Table 9.1.2 (toxicity profile table).

870.4300a Chronic Toxicity/Carcinogenicity Study - rat

See Section 4.5 (Chronic Toxicity), above for the executive summaries.

870.4200b Carcinogenicity (feeding) - Mouse

(1) In a mouse oncogenicity study (MRID No. 00115733), oxadiazon (tech., 99.3% a.i.) was administered in the diet to CD-1 mice (70/sex/group) for up to 105 weeks at 0, 100, 300, 1000, or 2000 ppm (equivalent to 0/0, 12/14, 37/44, 122/143, or 254/296 mg/kg/day [M/F], respectively).

At 2000 ppm, significantly decreased survival (and a dose-related positive trend for decreased survival) were observed in males (at termination, 43%, 24%, 36%, 27% and 4%, control to high dose) and in females (at termination, 56%, 41%, 53%, 43% and 29%). During the first 26 weeks of treatment, 29/70 high-dose males died or were sacrificed *in extremis*. It was stated that these animals were generally pale, inactive, weak, hypothermic and exhibited tremor and piloerection. Thoracic serosanguineous fluid was observed in these males at gross necropsy (15/29 treated vs 6/70 total controls affected and 1 of 2 controls that died by week 26). At histological examination, the following were also observed (# of animals): hypercellular spleens (18); diffuse, necrotic myocarditis (20); periacinar hepatocytic pallor (12); hepatic single cell necrosis (16); and pigmented Kupffer cells (8). An increase ($p<0.05$ or 0.01) in the total incidence of distended abdomen was observed at various intervals in all treated males (80-90% treated vs 60-61% controls). Pale eyes were observed in females (50-60% treated vs 31% controls). At 1000 and 2000 ppm, increased ($p<0.05$ or 0.01) incidence of pallor was observed (40-46% treated vs 21% controls) during the study. At 2000 ppm, body weights were reduced in males at week 104 (↓12%, not analyzed statistically). Reductions ($p<0.05$ or 0.01) in mean body weight gain were observed in the males during weeks 1-13 (↓13%) and for weeks 0-104 (↓26%); during weeks 66-92, weight loss was greater at high dose than controls (-7 g vs. -2 g, respectively). Slight anemia, as indicated by decreased ($p<0.05$, 0.01, or 0.001) hematocrit (-5 to -30%), hemoglobin (-6 to -28%), and erythrocyte count (-12 to -32%), was observed in the 1000 ppm males and 2000 ppm males and females. Neutrophil count was slightly increased at 2000 ppm in males (-83%) and females (-117%) at termination,

possibly reflecting a mild inflammatory response.

Increases ($p<0.05$, 0.01, or 0.001) with respect to concurrent controls were observed in absolute and relative (to body weight) liver weights in all male treatment groups (+45%/+52%, +46%/+57%, +107%/+120% and +86%/+120%) and in the 1000 and 2000 ppm female groups (+48/+53% and +103%/+102%). At gross necropsy, increased incidence of hepatic pale areas/foci and masses were observed in all male groups when excluding animals that died before week 27 (pale areas/foci 36%-59% treated vs 4% controls; masses 41%-47% treated vs 27% controls) and all female groups (pale areas/foci 11%-19% treated vs 7% controls; masses 10%-26% treated vs 3% controls). In addition, raised areas in the liver were observed in the 300, 1000, and 2000 ppm females (10-11% vs 1% control). Increases in large, eosinophilic hepatocytes were observed in all male and female groups without a clear dose-response (7-23 treated affected vs 0-3 controls, N = 70, all groups). Slight to moderate hepatic amyloidosis was increased in all male treatment groups (9-22 treated affected vs. 0 controls) and in high-dose females (12/70 treated vs 3/70 controls). Increased incidence of pigmented Kupffer cells (7/41 treated vs 0/70 controls) were observed in males that did not die by week 26. Food consumption, food efficiency, and water consumption (visually inspected, only) for both sexes at all doses were unaffected by treatment with oxadiazon at any tested dose. **The systemic toxicity LOAEL is ≤100 ppm for males and females (equivalent to 12/14 mg/kg/day [M/F]) based on clinical signs, gross and microscopic liver lesions in both sexes, and increased liver weights in males. The systemic toxicity NOAEL is <100 ppm.**

Under the conditions of this study, there was an increased incidence of hepatocellular neoplasms in males and females. Incidences of hepatocellular adenomas were increased ($p<0.05$, 0.01, or 0.001) in all groups of treated males (27.9%, 51.4%, 68.6%, 56.5% and 53.7%-68.6%, control to high dose) and females (4.4%, 18.8%, 25.7%, 32.9% and 41.2%) treatment groups. These were outside of historical control ranges of males (0-12%) in all groups, including controls, and of females (0-14%) for all treated groups. The incidences of adenocarcinomas were increased ($p<0.05$ or not significant) in all male treatment groups (7.4%, 20.0%, 24.3%, 24.6% and 24.4%, control to high dose) and in the 1000 and 2000 ppm female groups (12.9% and 10.3% vs 1.5%, controls). The incidences were outside of historical control ranges for males (0-8%) in all treatment groups and females (0-6%) at ≥1000 ppm. The incidences of combined adenomas and adenocarcinomas were increased ($p<0.05$, 0.01, or 0.001) in all male (29,4%, 57.1%, 74.3%, 63.8% and 68.3%) and female (5.9%, 18.8%, 27.1%, 38.6% and 47.1%) treatment groups (no historical controls provided for combined neoplasms). Dosing was considered adequate based on the finding of liver toxicity at all doses.

The submitted study is classified as **Acceptable/guideline (870.4200b)** and satisfies the guideline requirements for a carcinogenicity study in mice.

(2) In a chronic/oncogenicity toxicity study (MRID 40993301), oxadiazon (tech., 95.9% a.i.) was administered to 80 ICR-JCL mice (80/sex/dose) in the diet at 0, 3, 10, 100 or 1000

ppm (equivalent to 0, 0.315, 1.09, 10.6 or 113 mg/kg/day for males or 0, 0.278, 0.92, 9.3 or 99 mg/kg/day for females) for 98-99 weeks (the study was scheduled to run for 104 weeks but due to deaths, it was terminated at 98-99 weeks). Clinical signs were monitored daily. Body weights were determined weekly for the first 26 weeks and biweekly, thereafter; food consumption was determined twice weekly for 8 cages (4 mice/cage). Groups of 9-10 mice/sex/group were sacrificed at weeks 52 and 98/99 were subjected to hematology, biochemistry, urinalysis and pathology analysis.

Dose selection was based on a preliminary 4-week range finding study with 0, 10, 100, 1000 or 3000 ppm. Liver weights were increased in males at 100, 1000 and 3000 ppm and in females at 1000 and 3000 ppm. Signs of anemia were reported for both sexes at $\geq$1000 ppm. Elevated GOT and GPT (indicative of hepatic toxicity) was also evident at 1000 and 3000 ppm (males) and 3000 ppm (females).

There were no consistent adverse effects on mortality, clinical signs, body weight or food consumption. Hematological parameters significantly affected in male mice were: decreased hematocrit, hemoglobin and erythrocyte counts (all exposure groups at week 52 but not at week 98); and decreased mean corpuscular volume and mean corpuscular hemoglobin (high-dose males at weeks 52 and 98). In females, significantly decreased hemoglobin, mean corpuscular volume and decreased mean corpuscular hemoglobin were observed at 1000 ppm after 52 weeks of treatment. The generalized changes in these blood elements are indicative of anemia which was most evident in the males at week 52. Significantly affected clinical chemistry parameters at 1000 ppm included: increased GLP, GOT, ALP and BUN (males and females) and at 100 ppm were: increased GLP and GOT (males). High-dose males also had brownish colored urine at week 52. Significantly increased liver weights (absolute/relative) were seen in high-dose males at weeks 52 and 98 and in high-dose females at week 98. Significant increases in absolute and relative adrenal (males, week 98) and kidney (females, week 98) weights were also seen at 1000 ppm. Non-neoplastic pathology at 1000 ppm included: increased centrilobular hepatocellular swelling (females); increased diffuse hepatocellular swelling (males); brown pigmentation in the liver and proximal tubules of the kidney (males and females); extramedullary hematopoiesis (females) diffuse hepatocellular necrosis (males) and increased auricular thrombus (males). At 100 ppm, increased diffuse hepatocellular swelling and brown pigmentation in the liver were also seen in the males. **The LOAEL is 100 ppm (10.6 mg/kg/day) based on anemia, hepatocellular swelling, necrosis and the formation of brown pigment in the liver and kidneys of male mice. This latter finding is consistent with the established mechanism of action of oxadiazon in plants, (*i.e.*, inhibition of porphyrin biosynthesis). The NOAEL is 10 ppm (1.09/0.92 mg/kg/day for males/females).**

Neoplastic findings were: significant increases ($p<0.05-<0.001$) in liver adenomas and carcinomas in males and females at 1000 ppm; liver adenomas and carcinomas were also significantly increased at 100 ppm in males.

The pathology report for this chronic/carcinogenicity study in the mouse was considered incomplete; thus, the overall study was listed as Supplementary. At this time, additional information is not being requested because the results are consistent with an acceptable mouse carcinogenicity study (MRID No. 00115733) that satisfies the guideline requirement. Similarly, the presence of liver neoplasms confirms the evidence of a carcinogenic effect seen in other mouse long-term studies (MRID No. 00044322 and 00115733). After review of the data from this study by the Cancer Assessment Review Committee (CARC), however, it was concluded that this deficiency did not compromise the integrity of the study or the interpretation of the results [see Cancer Assessment Document--Evaluation of the Carcinogenic Potential of Oxadiazon (Third Review), dated April 2001]. Using this rationale, the study is now upgraded and listed as **Acceptable/guideline (870.4200b)**.

(3) In an oral mouse oncogenicity study (MRID 00044322), oxadiazon (tech. 95.5% a.i.) was administered in the diet to CD-1 mice (60/sex/group) for up to 104 weeks at 0, 300, 1000 or 2000 ppm (equivalent to 0/0, 48/62, 153/201, and 319/417 mg/kg/day [M/F], respectively. Actual daily dosage may have been slightly lower, based on the analytical diet concentrations). At study initiation, high-dose animals received 3000 ppm diets. Due to high mortality, the compound was removed from the high-dose diet for weeks 2 and 3, then dosing was re-initiated at 2000 ppm. Animals that died during weeks 1-5 (10 males, 3 females) were replaced with parallel treated animals or control replacement animals that had not previously received the test article. No interim sacrifice was performed.

Toxicity to the liver was observed at all doses. At 300 ppm, statistically significantly increased serum alkaline phosphatase (+60% above controls) and ALT or SGPT (+270%) in females, along with a non-significant increase in AST or SGOT (+76%, females) and ALT (+75%, males), and statistically significant increases in abs/rel liver weights in both males (+26%/+34%) and females (+50%/+60%) were observed. These parameters usually showed dose-dependent increases at $\geq$1000 ppm. Grossly visible liver masses (combined males/females 38% vs. 9%, controls) and liver microscopic lesions (bile duct proliferation, pigmented macrophages, diffuse hepatocellular hyperplasia, nodular hyperplasia, nodular hypertrophy and centrilobular hypertrophy) were increased at $\geq$300 ppm in both sexes. Some of these lesions did not show a dose-response, but were still considered treatment-related. At 1000 ppm, significantly increased serum alkaline phosphatase (+620%), AST (+104%), ALT (+218%) and cholesterol (+82%) were observed in males, and possibly lenticular degeneration in the eyes of males (10% vs. 0, controls). At 2000 ppm, most of these parameters showed additional increases and significantly increased cholesterol in females (+81%), increased lenticular degeneration in the eyes of males (25% vs. 0%, controls) and liver focal necrosis in males (54% vs. 35%, controls) and females (41% vs. 25%, controls) were also observed. A 16% decrease in hematocrit in males was considered of equivocal biological significance. Survival (after lowering of high dose to 2000 ppm), clinical signs, body weights, food consumption/efficiency and urine occult blood in both sexes were unaffected at all dose levels. **The systemic toxicity LOAEL is $\leq$300 ppm (approximately 48/62 [M/F] mg/kg/day) based on increased liver effects in both sexes.**

The systemic toxicity NOAEL is <300 ppm.

Under the conditions of this study, there was evidence of an increased incidence of hepatocellular carcinoma in both sexes. The increase was significant ($p<0.01$) in both sexes at 1000 (males - 24/60 or 40% vs 5/60 or 8.3%, controls; females - 12/61 or 19.7% vs 1/60 or 1.7%, controls) and 2000 ppm (27/69 or 39.1%, males and 13/63 or 20.6%, females). The incidence at 300 ppm in both males (7/60 or 11.7%) and females (4/60 or 6.7%) was not significant. Dosing was considered adequate based on the finding of liver toxicity at all doses.

The submitted study is classified as **Unacceptable/guideline (870.4200b).** Although several study deficiencies were identified, the additional information is not being requested at this time because the results are consistent with an acceptable mouse carcinogenicity study (MRID 00157780; also under MRID 00149003) that satisfies the guideline requirement. In the current study, the following were noted: (1) the summary tables of the gross pathology findings (Tables 9 and 10) were illegible in the only study copy available for review and (2) it was unclear from the study report what system of classification of liver proliferative and neoplastic microscopic lesions were used in this study compared to current conventions of classification. Although hepatocellular carcinomas were increased in treated animals, no adenomas were reported, which are generally observed as part of the tumor progression.

4.7 Mutagenicity

Adequacy of data base for Mutagenicity: The data base for mutagenicity is considered adequate based on pre-1991 mutagenicity guidelines. Overall, the available data indicate that oxadiazon is not mutagenic, but does cause neoplastic cell transformation *in vitro*. The acceptable bacterial assays conducted with 97.49% technical oxadiazon were negative. Similarly, neither 95.5% nor recrystallized oxadiazon (100%) were mutagenic or clastogenic in cultured mammalian cells and did not cause UDS in primary rat hepatocytes. There is, however, evidence that oxadiazon induced neoplastic transformation in Syrian hamster kidney cells both in the presence and the absence of S9 activation. This positive finding is consistent with the evidence from the mouse and rat long-term bioassays in which the incidence of liver tumors was increased.

Gene Mutation

870.5100 - Bacterial Reverse Gene Mutation Assay and 870.5500 - Bacterial DNA Repair Assay MRID 00069893 Acceptable/guideline	Doses tested: In *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 and *Escherichia coli* strain WP2 hcr-, 100-2500 μg/plate and 10-1000 μg/plate w/o S9 activation and 10-1000 μg/plate w/S9. *Bacillis subtilis* strains H17 and M45, 20-2000 μg/plate w/o activation. Negative. Cytotoxicity not observed.

870.5100 - Bacterial Reverse Gene Mutation MRID 41871701 Acceptable/guideline	Doses tested: In *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100, 50-5000 μg/plate w/ and w/o S9 activation. Negative up to cytotoxic doses (3330 μg/plate) in absence of S9 and up to 5000 μg/plate in presence of S9 (not cytotoxic at any dose tested +S9). Insoluble at ≥ 500 μg/plate.
870.5300 - *In Vitro* Mammalian Gene Mutation Assay MRID 00115726 Acceptable/guideline	Doses tested: In L5178Y TK+/- mouse lymphoma cells, 15.6, 31.3, 250, 500 or 1000 μg/mL (trial 1) and 50, 300, 600, 800 or 1000 μg/mL (trial 2) w/o S9; 3.91, 7.81, 15.6, 31.3 or 62.5 μg/mL (trial 1), 20, 30, 40, 60, 80 or 100 μg/mL (trial 2) and 100, 120, 140, 160, 180 or 200 μg//L (trial 3) w/ S9. Negative up to cytotoxic levels (1000 μg/mL w/S9 and 200 μg/mL w/o S9). Insoluble at ≥ 62.5 μg/mL.
870.5300 - *In Vitro* Mammalian Gene Mutation Assay MRID 00115729 Acceptable/guideline	Doses tested: In L5178Y TK+/- mouse lymphoma cells, oxadiazon recrystallise (100% a.i.) 31.3, 62.5, 125, 250, 500 or 1000 μg/mL w/o S9 and 15.6, 31.3, 62.5, 125 or 250 μg/mL w/ S9. Negative up to cytotoxic doses (1000 μg/mL w/o S9 and 250 μg/mL w/S9). Insoluble at 250 μg/mL.

Cytogenetics

870.5375 - *In Vitro* Mammalian Cell Chromosomal Aberration Assay MRID 00115728 Acceptable/guideline	Doses tested: In Chinese hamster ovary cells, oxadiazon recrystallise (100% a.i.) at 2.0, 6.7, 20, 66.7, 200, 667 or 2000 μg/mL w/o S9 and 0.667, 2.0, 6.7, 20.0, 66.7, 200, 667 or 1000 μg/mL w/S9 (trial 1); and at 200, 300, 400, 500 or 600 μg/mL w/S9 (trial 2). Negative up to cytotoxic concentrations (200 μg/mL w/o S9 and ≥500 μg/mL w/S9). Insoluble at 667 μg/mL w/o S9 and 200 μg/mL w/S9.
870.5375 - *In Vitro* Mammalian Cell Chromosomal Aberration Assay MRID 00115730 Acceptable/guideline	Doses tested: oxadiazon tech. (95.5% a.i.) in Chinese Hamster ovary cells at 0.416, 1.25, 4.16, 12.5, 41.6 or 125 μg/mL (trial 1) and 12.5, 25, 50 or 75 μg/ml w/o S9 (trial 2) and 1.25, 4.16, 41.6 or 125 μg/mL w/S9 (trial 2). Negative up to cytotoxic concentrations (≥75 μg/mL w/o S9 and ≥41.6 μg/mL w/S9). Insoluble at 416 μg/mL.
870.5395 - Mammalian Erythrocyte Micronucleus Test MRID 00073288 Unacceptable/guideline (not upgradable)	Doses tested: In CD-1 mice, 0, 500, 100 or 200 mg/kg (2 gavage doses 24 hr apart). Harvested 6 hr after second dose. Negative; however was unacceptable because the 6 hr sampling time could have missed an effect and no evidence that target tissue was reached.
870.5395 - Mammalian Erythrocyte Micronucleus Test MRID 00073289 Unacceptable/guideline (not upgradable)	Doses tested: In CD-1 mice, 0, 500, 1000 or 2000 mg/kg, 2 gavage doses 24 hrs apart. Harvest 6 hrs post-treatment. Negative; however was unacceptable because the 6 hr sampling time could have missed an effect and no evidence that target tissue was reached.
870.5395 - Mammalian Erythrocyte Micronucleus Test MRID 00073290 Unacceptable/guideline (not upgradable)	Doses tested: In CD-1 mice, 0, 500, 1000 or 2000 mg/kg, 2 gavage doses 24 hrs apart. Harvest 6 hrs post-treatment. Negative; however was unacceptable because the 6 hr sampling time could have missed an effect. Clinical signs of toxicity observed at 2000 mg/kg.

Other Genotoxicity

870.5550 - Unscheduled DNA Synthesis MRID 00115723 Acceptable/guideline	Doses tested: In primary rat hepatocytes, 1.0, 2.5, 5.0, 10, 25, 50 250 or 1000 μg/mL, 18 hr exposure. Negative up to cytotoxic concentrations (100-500 μg/ml).
870.5550 - Unscheduled DNA Synthesis MRID 00115727 Acceptable/guideline	Doses tested: In primary rat hepatocytes, 0.5, 1.0, 2.0, 5.0, 10, 25 or 50 μg/mL. Negative up to cytotoxic concentrations (≥100 μg/ml).

Nonguideline - *In vitro* cell transformation MRID 00115703 Acceptable/non-guideline	Doses tested: In Syrian hamster BHK21 C13/HRC1 cells, 12.5, 25, 50, 100 or 200 μg technical oxadiazon/mL and 25, 50, 100, 200 or 400 μg recrystallized oxadiazon; both tested w/ and w/o S9 activation. Positive in the presence and absence of S9 metabolic activation. At the LD_{50} or HDT, transformation frequencies exceeded 5X solvent control w/ and w/o S9 for both oxadiazon and recrystallized oxadiazon.

4.8 Neurotoxicity

Adequacy of data base for neurotoxicity: These studies are not required at this time because there was no evidence of potential neurotoxicity in the database.

4.9 Metabolism and Dermal Penetration

Adequacy of data base for metabolism and dermal penetration: The data base for metabolism is considered to be complete. No additional studies are required at this time. In rats, oxadiazon was extensively metabolized and most was excreted in both urine and feces during the 7 days following dosing. Although at the low dose (5 mg/kg), only a small amount of parent compound was excreted, at high dose (500 mg/kg), as much as 53% of unchanged oxadiazon was excreted in the feces. Females tended to excrete more of the administered dose in the urine than males. A total of 18 metabolites were identified in the urine and feces.

Two studies not required by the guidelines were also submitted. In a dermal absorption study in the rat, penetration was shown to be less than 10% in rats exposed for up to 10 hrs. A 14-day dietary study in the rat was also submitted in which peroxisomal proliferative effects were examined. In this study, liver enlargement, proliferation of hepatocyte peroxisomes and induction of several peroxisomal enzymes were observed. However, activity of catalase, usually induced by such compounds, was decreased by oxadiazon treatment. Hepatocellular proliferation was not evaluated.

In addition to the Executive Summaries provided below, the metabolism and dermal penetration studies are summarized in capsule form in Section 9.0 (Appendix), Table 9.1.2 (toxicity profile table).

870.7485 Metabolism - Rat

In a metabolism/pharmacokinetic study (MRIDs 42324701, 42663601), five Crl:CD(SD)BR rats of each sex were dosed with ^{14}C-labeled oxadiazon at a single oral dose of 5 mg/kg or 500 mg/kg, and multiple doses of 5 mg/kg unlabeled oxadiazon for 14 days followed by a single oral dose of labeled oxadiazon at 5 mg/kg on day 15. At low doses (5 mg/kg, single or multiple), oxadiazon was completely absorbed, metabolized and excreted in the urine and feces; virtually no free oxadiazon was found in the urine. At this

dose, the rates and routes of excretion of radioactivity were similar. At 500 mg/kg, the rate of excretion was affected but the route was not. The excretion of radioactivity into the urine and the feces was sex dependent and the tissue residues were very low in all tissues except liver and fat. Over a 7-day period, 85 to 93% of the test compound administered was excreted in the urine and feces. The radioactivity recovered in the urine, feces and tissues exceeded 94% of the dose and was sex-related. Females excreted more radioactivity in the urine than males. The metabolism of oxadiazon in rats was extensive, but the benzene and pyrozolidine rings were not modified. Eighteen (18) metabolites were identified in the urine and feces. Four urinary and 5 fecal metabolites were present at levels greater than 1% of the dose. Among the 9 metabolites, U2, U7 and U10 from the urine correspond to F2, F7 and F9 of the feces. Female rats were efficient metabolizers and the urine was unique in that metabolites U4 and U5 were excreted in the urine only. In addition to 5 fecal metabolites, intact oxadiazon was present in feces only and was dose-related. At the high dose more than 53% of the administered radioactivity was intact oxadiazon in the feces; at 5 mg/kg, not more than 4.8% of the dose was intact oxadiazon in the feces. This observation is consistent with extensive absorption followed by excretion in the feces by way of the bile.

This study is classified **Acceptable/guideline** and satisfies the Guideline requirements **(870.7385)** for a metabolism study for oxadiazon in the rat.

870.7600 Dermal Absorption - Rat

In a dermal penetration study (MRID 44588101), ^{14}C-oxadiazon (99.6% a.i., radiochemical purity, mixed with unlabelled oxadiazon technical, 96% a.i.) in 1% aqueous carboxymethyl cellulose was administered dermally to groups of 24 male Sprague Dawley rats/dose at 5.45, 39.2 or 523 μg/cm^2 for exposure durations of 0.5, 1, 2, 4, 10 or 24 hours per dose (4 rats/exposure time). Urine and feces were collected; skin was excised and blood, residual urine and carcasses were collected and analyzed. Recovery of radioactivity ranged from 83.2% to 106% of administered dose.

The quantity of oxadiazon in washed skin during the exposure phase ranged from 0.06-0.38, 0.59-3.31 or 2.88-15.32 μg/cm^2 at the low, mid or high dose, respectively. As a percentage of the administered dose, these were equivalent to 1.09%-6.89%, 1.50%-8.45% or 0.55%-2.93% (low to high dose, respectively). In general, the amount of absorbed test material was not detectable during the first 2 hours of exposure. Absorption (μg/cm^2) was low throughout exposure and ranged from 0.06-0.6, 0.05-2.00 or 0.05-2.62 μg/cm^2 (low to high dose, respectively) at 4 to 24 hours; as a percent of the administered dose, these were equivalent to 1.11%-11.0%, 0.39%-5.11% or 0.01%-0.50%, respectively. The percent of test material on the skin versus the percent absorbed at 10 hours was 6.05% vs. 2.65% (5.45 μg/cm^2), 4.71% vs. 0.63% (39.2 μg/cm^2) and 1.03% vs. 0.05% (523 μg/cm^2). Since the percent of dose absorbed decreased with increasing dose and the quantity absorbed was essentially the same, the results indicate that absorption but not dermal uptake was saturated at 39.2 and 523 μg/cm^2.

This study is classified **Acceptable/guideline**; it satisfies the guideline requirement for a dermal penetration study **(870.7600)** in the rat.

4.10 Special/Other Studies

A 14-day dietary study evaluating peroxisomal proliferation by oxadiazon in the rat was submitted. In addition to the Executive Summary provided below, this study is summarized in capsule form in Section 9.0 (Appendix), Table 9.1.2 (toxicity profile table).

In a special mechanistic study (MRID No. 42310001), oxadiazon (tech., 95.6% a.i.) was orally administered to groups of male Sprague-Dawley rats (10 rats/dose) at 0, 20, 200 or 500 mg/kg/day for 14 days. Clinical signs were monitored daily. Body weights, food consumption and water consumption were determined daily. After 14 days of treatment, animals were sacrificed and organ weights were determined. Livers were prepared for microscopic examination (high-dose only) and liver homogenates from all dose levels were assessed for protein, glucose 6-phosphatase, catalase, palmitoyl CoA oxidation, palmitoyl carnitine transferase and acetyl carnitine transferase.

There were no adverse effects on mortality, clinical signs, body weight or food and water consumption. Absolute and relative liver weights were significantly ($p<0.05$) increased at 200 and 500 mg/kg/day. Thyroid and kidney weights were unaffected by treatment. Significant ($p<0.05$) effects on liver biochemistry at 200 and 500 mg/kg/day were: decreased catalase (-62 and -72%, respectively); increased palmitoyl CoA oxidation (+43 and + 98%, respectively); increased palmitoyl carnitine transferase (+92 and 113%, respectively); and increased acetyl carnitine transferase (+296 and 569%, respectively). Nonsignificant changes noted for these parameters in the 20-mg/kg/day group were: increased palmitoyl CoA oxidation (+13%); increased palmitoyl carnitine transferase (+6%); and increased acetyl carnitine transferase (+57%). In addition, glucose 6-phosphatase was significantly inhibited at 500 mg/kg/day. Data for these enzyme levels indicate dose-dependent increases in peroxisomal enzyme activity (in particular palmitoyl Co A and acetyl carnitine transferase as well as the mitochondrial associated palmitoyl carnitine transferase). Ultrastructural changes seen after treatment with 500 mg/kg/day included: peroxisome proliferation, increased lipids, sinusoidal dilation, and rough endoplasmic reticulum damage. The generalized changes in the enzyme levels indicate dose-dependent increases in peroxisomal enzyme activity (in particular palmitoyl Co A and acetyl carnitine transferase as well as the mitochondrial associated palmitoyl carnitine transferase). **The LOAEL is 20 mg/kg/day (lowest treatment level) based on increased peroxisomal enzyme activity (in particular palmitoyl Co A and acetyl carnitine transferase) at all dose levels. This study does not define a NOAEL (<20 mg/kg/day).**

This special peroxisome proliferation study in the rat is **Acceptable/non-guideline** for the purpose for which it was intended.

5.0 TOXICITY ENDPOINT SELECTION

5.1 See Section 9.2 for Endpoint Selection Table.

5.2 Dermal Absorption

Dermal Absorption Factor: 9 %

The HIARC (December 7, 2000) determined that a dermal absorption factor of 9% should be used for risk assessment. The dermal absorption factor is based on the dermal absorption observed (6.05% absorbed + 2.65% bound = 8.7%) after a 10 hr exposure in a rat dermal absorption study (MRID 44588101).

The dermal absorption factor is required for the short-term, intermediate-term and long-term dermal risk assessments since oral doses were administered in the study selected for these exposure periods (rat developmental toxicity study).

5.3 Classification of Carcinogenic Potential

5.3.1 Discussion of Findings

Oxadiazon was evaluated for carcinogenicity for the third time by the HED Cancer Assessment Review Committee on March 7, 2001 (HED Document No. 014555). This reevaluation was prompted by the submission of a mouse and a rat carcinogenicity study that were not previously available to the Agency for review. A treatment-related increase in the incidence of hepatocellular benign and malignant tumors was identified in these new studies in male Wistar rats (MRID 40993401) and in male and female ICR-JCL mice (MRID 40993301). The results of the new studies are consistent with those of the previously reviewed studies on F344 rats (MRIDs 00149003, 00157780) and CD-1 mice (MRIDs 00044322, 00115733). The findings of these studies are summarized above in the Hazard Assessment (see Section 4.6). The quantitative risk [Q_1^* $(mg/kg/day)^{-1}$] was also recalculated as shown below, based on evaluation of the new data (Memorandum from L. Brunsman to N. McCarroll dated February 1, 2001). The available mechanistic data on the peroxisomal proliferative properties of oxadiazon were considered insufficient to support a threshold mechanism for hepatocellular carcinogenesis (see Section 7.0, below).

5.3.2 Classification of Carcinogenic Potential

Oxadiazon is classified as “likely to be a human carcinogen”, using the classification system of the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999). Hepatocellular tumors were identified in two species and 2 sexes (in mice; only males showed significant increases in rats).

5.3.3 Quantification of Carcinogenic Potential

The Q_1^* $(mg/kg/day)^{-1}$ calculated for oxadiazon is 7.11×10^{-2} mg/kg/day, based on male mouse liver adenoma and/or carcinoma combined tumor rates from the 98-week dietary study (MRID 40993301).

6.0 FQPA CONSIDERATIONS

6.1 Special Sensitivity to Infants and Children

In the rabbit developmental study, there was no evidence of either a quantitative or qualitative increase in the sensitivity of fetuses. However, in the rat developmental study, very little maternal toxicity (small but significant decrease in body weight, -2% and decrease in body weight gain, -10%) was seen at the maternal and developmental LOAEL (40 mg/kg/day). By contrast, effects on offspring at this LOAEL were severe (increased post- implantation loss and late resorptions and decreased fetal weight). Neonatal effects (LOAEL of 38 mg/kg/day, based on neonatal losses) in the dose range-finding phase of the two generation reproduction study in rats were attributable to maternal effects (i.e., inactive mammary tissue) at that dose. **Based on weight-of-the-evidence considerations, the Committee concluded that the overall data provide no clear evidence of either a qualitative or quantitative increase in susceptibility of rats or rabbits to *in utero* and/or postnatal oxadiazon exposure.**

6.2 Recommendation for a Developmental Neurotoxicity Study

The HIARC **recommended against** requiring a developmental neurotoxicity study. This decision was based on results showing no evidence of neurotoxicity in any study in the database which included: chronic (rats, mice, dogs), subchronic (rat or rabbit), reproduction (rat) or developmental (rat or rabbit) studies.

7.0 OTHER ISSUES

Many compounds that induce hepatic peroxisomal proliferation also are hepatic carcinogens. Because the special mechanistic study demonstrated that oxadiazon caused hepatocellular peroxisomal proliferation, the MTARC evaluated the complete database to determine whether it supported peroxisomal proliferation as a mechanism of action for hepatocellular carcinogenesis in rats and mice (meeting of February 8, 2001). Based on weight-of-the-evidence considerations, the MTARC determined that although oxadiazon did not show mutagenic potential and peroxisomal proliferation may be a possible mode of action for hepatocellular carcinogenesis by oxadiazon, the data were insufficient to support this mechanism. The weaknesses in the database included: (1) no cell proliferation data were provided for rats or mice; (2) a good concordance between the dose-response for peroxisomal enzymatic activity and tumor formation was not observed and (3) the role of decreased catalase activity, which is generally increased by peroxisomal proliferator compounds, was not explained by the authors of the submitted mechanistic study.

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9.0 APPENDICES

Tables for Use in Risk Assessment

9.1 Toxicity Profile Summary Tables

9.1.1 Acute Toxicity Table - See Section 4.1

9.1.2 Subchronic, Chronic and Other Toxicity Tables

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
SUBCHRONIC TOXICITY STUDIES		
870.3100 90-Day oral toxicity (CD rat)	00111804 (1970) Acceptable/guideline 0, 25, 100 or 1000 mg/kg/d (diet)	NOAEL = 25 mg/kg/day LOAEL = 100 mg/kg/day based on decreased body weight, increased liver weight, hematological changes and clinical chemistry and pathological changes associated with liver damage.
870.3150 90-Day oral toxicity in (Beagle dog)	00111805 (1970) Acceptable/guideline 0, 25, 100 or 1000 mg/kg/d (capsule)	NOAEL <25 mg/kg/day LOAEL ≤25 mg/kg/day based on increased thyroid weights in males.
870.3200 21-Day dermal toxicity (NZW rabbit)	41863602 (1991) Acceptable/guideline 0, 100, 500 or 1000 mg/kg/day	NOAEL ≥ 1000 mg/kg/day. LOAEL > 1000 mg/kg/day.
DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES		
870.3700a Prenatal developmental (SD rat)	40470202 (1987) Acceptable/guideline 0, 3, 12 or 40 mg/kg/day (gavage)	**Maternal** NOAEL = 12 mg/kg/day. LOAEL = 40 mg/kg/day based on decreased body weight/weight gain. **Developmental** NOAEL = 12 mg/kg/day LOAEL = 40 mg/kg/day based on increased fetal resorptions/implantation loss, decreased pup weight and increased incidence of incomplete ossification.
870.3700b Prenatal developmental (NZW rabbit)	40470201 (1987) Acceptable/guideline 0, 20, 60 or 180 mg/kg/day (gavage)	**Maternal** NOAEL = 20 mg/kg/day LOAEL = 60 mg/kg/day based on transient weight loss during the first week of treatment. **Developmental** NOAEL = 60 mg/kg/day LOAEL = 180 mg/kg/day based on increased postimplantation loss and late resorptions, decreased fetal weight and increased bilateral hind-limb flexure.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3800 Reproduction and fertility effects (CD rat)	41239801 (1988) Acceptable/guideline 0, 20, 60 or 200 ppm (M/F 0, 1.5/1.84, 4.65/5.63 or 15.50/18.20 mg/kg/day, premating)	**Parental/Systemic** NOAEL ≥ 15.5 mg/kg/day LOAEL >15.5 mg/kg/day (decreased gestational weight gain in RF study at 38 mg/kg/day). **Reproductive** NOAEL ≥ 15.5 mg/kg/day LOAEL > 15.5 mg/kg/day (inactive mammary tissue, fetal/neonatal mortality in the RF study at 38 mg/kg/day). **Offspring** NOAEL ≥ 15.5 mg/kg/day LOAEL > 15.5 mg/kg/day (fetal/neonatal mortality in the RF study at 38 mg/kg/day).
CHRONIC TOXICITY AND CARCINOGENICITY STUDIES		
870.4100a Chronic toxicity (rat)	See 870.4300, Combined chronic toxicity/carcinogenicity	
870.4100b Chronic toxicity (Beagle dog)	41326401(1989) Acceptable/guideline 0, 5, 20 or 60 mg/kg/day (capsule)	NOAEL = 5 mg/kg/day LOAEL = 20 mg/kg/day based on increased liver weight.
870.4200 Carcinogenicity (CD-1 mouse)	00044322 (1980) Unacceptable/guideline 0, 300, 1000 or 2000 ppm (M/F 0, 48/62, 153/201 or 319/417 mg/kg/day), in diet	NOAEL <48 mg/kg/day LOAEL ≤48 mg/kg/day based on increased liver weight, serum enzymes related to liver damage and microscopic pathology in the liver of both sexes. **Evidence of carcinogenicity**- increased incidence of hepatocellular carcinoma, both sexes at ≥48/62 mg/kg/day.
870.4200 Carcinogenicity (CD-1 mouse)	00115733 (1982) Acceptable/guideline 0, 100, 300, 1000 or 2000 ppm (M/F 0, 12/14, 37/44, 122/143 or 254/296 mg/kg/day), in diet	NOAEL ≤12 mg/kg/day LOAEL < 12 mg/kg/day based on clinical signs, increased liver weights in males and increased microscopic pathology in the liver of both sexes. **Evidence of carcinogenicity** - increased incidence of hepatocellular neoplasms (adenoma, combined adenoma/carcinoma) in both sexes at all doses tested (carcinoma alone increased in all male groups and at ≥143 mg/kg/day in females).
870.4200 Carcinogenicity (ICR-JCL mouse)	40993301 (1987) Acceptable/guideline 0, 3, 10, 100 or 1000 ppm (M/F 0, 0.315/0.278, 1.09/0.92, 10.6/9.3 or 113/99 mg/kg/day), in diet	NOAEL = 1.09 mg/kg/day LOAEL = 10.6 mg/kg/day based on anemia and microscopic lesions in the liver and kidneys (all in males). **Evidence of carcinogenicity** - increased incidence of hepatocellular neoplasms (adenomas, carcinomas and combined adenomas/carcinomas in males at ≥10.6 mg/kg/day and in females at 99 mg/kg/day).

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.4300 Combined chronic toxicity/carcinogenicity (F344 rat)	00149003, 00157780 (1982, 1986) Acceptable/guideline 0, 10, 100, 1000 or 3000 ppm (M/F 0, 0.5/0.6, 5.9/4.8, 50.9/60.9 or 163.1/192.7 mg/kg/day, in diet	NOAEL = 0.5 mg/kg/day LOAEL = 4.8 mg/kg/day based on increased liver weights in both sexes and increased total serum protein in females. **Evidence of carcinogenicity** - increased incidence of hepatocellular neoplasms in males (adenomas and combined adenomas/carcinomas in males at ≥50.9 mg/kg/day).
870.4300 Combined chronic toxicity/carcinogenicity (Wistar rat)	40993401 (1987) Acceptable/guideline 0, 3, 10, 100 or 1000 ppm (M/F 0, 0.106/0.131, 0.36/0.44, 3.5/4.2 or 39/44 mg/kg/day)	NOAEL = 0.36 mg/kg/day LOAEL = 3.5 mg/kg/day based on increased incidence of hepatocellular centrilobular swelling in males. **Evidence of carcinogenicity**-increased incidence of hepatocellular neoplasms in males (adenomas and combined adenomas/carcinomas at ≥4.2 mg/kg/day and carcinomas at 39 mg/kg/day).
MUTAGENICITY AND CELL TRANSFORMATION STUDIES		
870.5100 Gene Mutation Bacterial reverse gene mutation assay and 870.5500 Bacterial DNA Repair Assay	00069893 (1976) Acceptable/guideline *S. typhimurium* and *E. coli* 100-2500 and 10-1000 μg/plate w/o S9 and 10-1000 μg/plate w/S9. *B. subtilis* 20-2000 μg/plate w/o S9.	Negative in *S. typhimurium* strains TA1535, TA1437, TA1538, TA98 and TA100; *E. coli* strain WP2 *hcr*$^-$ and *B. subtilis* strains H17 and M45 (cytotoxicity not observed).
870.5100 Gene Mutation Bacterial reverse gene mutation assay	41871701 (1991) Acceptable/guideline 50-5000 μg/plate w/o or w/S9.	Negative in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 (cytotoxicity observed at ≥3330 μg/plate w/o S9 but not w/S9). Insoluble at ≥500 μg/plate.
870.5300 Gene Mutation *In vitro* mammalian cell forward gene mutation assay	00115726 (1982) Acceptable/guideline 15.6-1000 μg/mL (Trial 1), 50-1000 μg/mL (Trial 2), both w/o S9; 3.91-62.5 (Trial 1), 20-100 (Trial 2) and 100-200 μg/mL (Trial 3), all w/S9.	Negative in L5178Y TK$^+$ mouse lymphoma cells (cytotoxicity observed at 1000 μg/mL w/o S9 and ≥200 μg/mL w/S9). Insoluble at ≥62.5 μg/mL.
870.5300 Gene Mutation *In vitro* mammalian cell forward gene mutation assay	00115729 (1982) Acceptable/guideline 31.3-1000 μg/mL w/o S9 and 15.6-250 μg/mL w/S9	Negative in L5178Y TK$^+$ mouse lymphoma cells (cytotoxicity observed at 1000 μg/mL w/o S9 and 250 μg/mL w/S9). Insoluble at 250 μg/mL.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.5375 Cytogenetics *In vitro* mammalian cell chromosomal aberration assay	00115728 (1982) Acceptable/guideline 2-2000 μg/mL w/o S9; 0.667-2000 μg/mL (Trial 1) and 200-600 μg/mL (Trial 2), both w/S9.	Negative in Chinese hamster ovary (CHO) cells (cytotoxicity observed at 200 μg/mL w/o S9 and 500 μg/mL w/S9). Insoluble at 667 μg/mL w/o S9 and 200 μg/mL w/S9.
870.5375 Cytogenetics *In vitro* mammalian cell chromosomal aberration assay	00115730 (1982) Acceptable/guideline 0.416-125 μg/mL (Trial 1) and 12.5-75 μg/mL (Trial 2), both w/o S9; 1.25-125 μg/mL w/S9 (trial 2).	Negative in Chinese hamster ovary (CHO) cells (cytotoxicity at 75 μg/mL w/o S9 and 41.6 μg/mL w/S9). Insoluble at 416 μg/mL.
870.5395 Cytogenetics Mammalian erythrocyte micronucleus test	0073288 (1980) Unacceptable/guideline (not upgradable) 0, 500, 1000 or 2000 mg/kg 100% oxadiazon	Negative up to limit dose of 2000 mg/kg, but early sampling time (6 hr post-dosing) may have missed peak time of mutagenic effect. No signs of toxicity were observed.
870.5395 Cytogenetics Mammalian erythrocyte micronucleus test	0073289 (1980) Unacceptable/guideline (not upgradable) 0, 500, 1000 or 2000 mg/kg	Negative up to limit dose of 2000 mg/kg , but early sampling time (6 hr post-dosing) may have missed peak time of mutagenic effect. No signs of toxicity were observed.
870.5395 Cytogenetics Mammalian erythrocyte micronucleus test	00732890 (1980) Unacceptable/guideline (not upgradable) 0, 500, 1000 or 2000 mg/kg 24865 RP (99%), an oxadiazon impurity	Negative up to limit dose of 2000 mg/kg, but early sampling time (6 hr post-dosing) may have missed peak time of mutagenic effect. Clinical signs of toxicity observed at $\geq$1000 mg/kg including 2 deaths at 2000 mg/kg.
870.5550 Other Effects Unscheduled DNA synthesis assay	00115723 (1982) Acceptable/guideline 1.0 to 1000 μg/mL	Negative in primary rat hepatocytes after 18 hrs (cytotoxicity observed at 100-500 μg/mL).
870.5550 Other Effects Unscheduled DNA synthesis assay	00115727 (1982) Acceptable/guideline 0.5 to 50 μg/mL	Negative in primary rat hepatocytes after 18 hrs (cytotoxicity observed at 50 μg/mL).

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
Nonguideline Other Effects *In vitro* cell transformation	00115703 (1982) Acceptable/nonguideline 12.5-200 μg/mL w/ and w/o S9 for technical oxadiazon; 25-400 μg/mL for recrystallized oxadiazon (100%) w/S9 or w/o S9.	Dose-related induction of cell transformation above background levels observed w/S9 and w/o S9 activation in Syrian hamster kidney cells (BHK21 C13/HRC1 cells) for both technical and recrystallized oxadiazon.
METABOLISM, DERMAL PENETRATION AND SPECIAL MECHANISTIC STUDIES		
870.7485 Metabolism and pharmacokinetics (Crl:CD(SD)BR rat)	42324701, 42663601 (1992, 1993) Acceptable/guideline 5 mg/kg ^{14}C-oxadiazon (single dose), 5 mg/kg (14-day dose of oxadiazon + 1 dose of ^{14}C-oxadiazon, day 15) or 500 mg/kg ^{14}C-oxadiazon (gavage)	At 5 mg/kg, oxadiazon is completely absorbed, metabolized and excreted in urine and feces (no parent compound in urine; <5% in feces. At 500 mg/kg, 53% of administered dose was excreted in feces as parent compound. For both groups, $\geq$83% of administered dose was excreted in urine and feces (total recovery $\geq$94%) by 7 days' post-dosing. Females tended to excrete more radioactivity in urine than males. Oxadiazon was metabolized primarily by hydroxylation and glucuronide conjugation, but benzene and pyrozolidine rings were not metabolized. A total of 18 metabolites were identified in urine and feces (4 urinary, 5 fecal metabolites present at >1% of administered dose).
870.7600 Dermal penetration (SD rat)	44588101(1996) Acceptable/guideline 5.45, 39.2 or 523 μg/cm^2 (exposure times of 0.5, 1, 2, 4, 10 or 24 hrs)	Total absorption 9% of administered dose following 10 hr exposure (6.05% in skin and 2.65% absorbed). Absorption but not dermal uptake saturated at 39.2 and 523 μg/cm^2.
Special studies (nonguideline) - Peroxisomal proliferation (SD rat)	42310001 (1991) Acceptable/nonguideline 0, 20, 200 or 500 mg/kg/day in diet for 14 days	NOAEL <20 mg/kg/day. LOAEL = 20 mg/kg/day, based on increased peroxisomal enzyme (palmitoyl CoA and acetylcarnitine transferase) activities. At 200 mg/kg/day, liver enlargement and at 500 mg/kg/day, ultrastructural changes (peroxisomal proliferation and microsomal alterations) were also observed. However, catalase was decreased by treatment.

9.2 Summary of Toxicological Dose and Endpoints for Oxadiazon for Use in Human Risk Assessment[1]

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOAEL= N/A UF = N/A		
	This risk assessment is not required at this time because there are no food or feed uses for Oxadiazon		
Chronic Dietary	NOAEL = N/A UF = N/A		
	This risk assessment is not required at this time because there are no food or feed uses for Oxadiazon		
Cancer	Q_1* of 7.11 x 10^{-2} $(mg/kg/day)^{-1}$in human equivalents[a], based on increased incidence of combined hepatocellular adenomas/carcinomas in male ICR-JCL mice.	"Possibly a human carcinogen", based on increased incidence of hepatocellular tumors in four of the five positive studies (two mouse studies and two rat studies) at doses that exceeded the maximum tolerated dose.	Combined Chronic Toxicity/ Carcinogenicity Studies in Rats MRID Nos. 00149003/00157780 and 40993401 Carcinogenicity Studies in Mice MRID Nos. 00115733 and 40993301 (increased liver tumors also observed in both sexes in an unacceptable mouse oncogenicity study, MRID 00044322).
Incidental Oral, Short-Term	NOAEL= 12 Maternal effects	Reduced body weight/body weight gain at 40 mg/kg/day (LOAEL).	Developmental Toxicity -Rat MRID No. 40470202
Incidental Oral, Intermediate-Term	NOAEL= 12 Maternal effects	Reduced body weight/body weight gain at 40 mg/kg/day (LOAEL).	Developmental Toxicity -Rat MRID No. 40470202
Dermal, Short-Term	NOAEL= 12 Developmental effects	Increased fetal resorptions/postimplantation loss, increased incidence of incomplete ossification at 40 mg/kg/day (LOAEL). For this risk assessment, the dermal absorption factor of 9% is applied.	Developmental Toxicity -Rat MRID No. 40470202

EXPOSURE	DOSE (mg/kg/day)	ENDPOINT	STUDY
Dermal, Intermediate-Term	NOAEL= 12 Developmental effect	Increased fetal resorptions/postimplantation loss, increased incidence of incomplete ossification at 40 mg/kg/day (LOAEL). For this risk assessment, the dermal absorption factor of 9% is applied.	Developmental Toxicity - Rat MRID No. 40470202
Dermal, Long-Term	NOAEL= 0.36	Increased centrilobular swelling in male livers at 3.5 mg/kg/day (LOAEL). For this risk assessment, the dermal absorption factor of 9% is applied.	Combined Chronic Feeding/ Oncogenicity - Rat MRID Nos. 40993401, 00149003/ 00157780
Inhalation, Short-Term	NOAEL= 12 Developmental effect	Increased fetal resorptions/postimplantation loss, increased incidence of incomplete ossification at 40 mg/kg/day (LOAEL). For this risk assessment, use a route-to-route extrapolation and a 100% absorption rate (default value).	Developmental Toxicity - Rat MRID No. 40470202
Inhalation, Intermediate-Term	NOAEL= 12 Developmental effect	Increased fetal resorptions/postimplantation loss, increased incidence of incomplete ossification at 40 mg/kg/day (LOAEL). For this risk assessment, use a route-to-route extrapolation and a 100% absorption rate (default value).	Developmental Toxicity - Rat MRID No. 40470202
Inhalation, Long-Term	NOAEL= 0.36	Increased centrilobular swelling in male livers at 3.5 mg/kg/day (LOAEL). Use a route-to-route extrapolation and a 100% absorption rate (default value)	Combined Chronic Feeding/ Oncogenicity - Rat MRID Nos. 40993401, 00149003/ 00157780

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